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Dupilumab-induced serum sickness-like reaction: an unusual adverse effect in a patient with atopic eczema

Editor

Dupilumab is a fully humanized Immunoglobulin-(Ig)-G4 antibody against the interleukin (IL)-4 α subunit of the IL-4 receptor and the IL-13 receptor.¹ In patients with atopic eczema (AE),

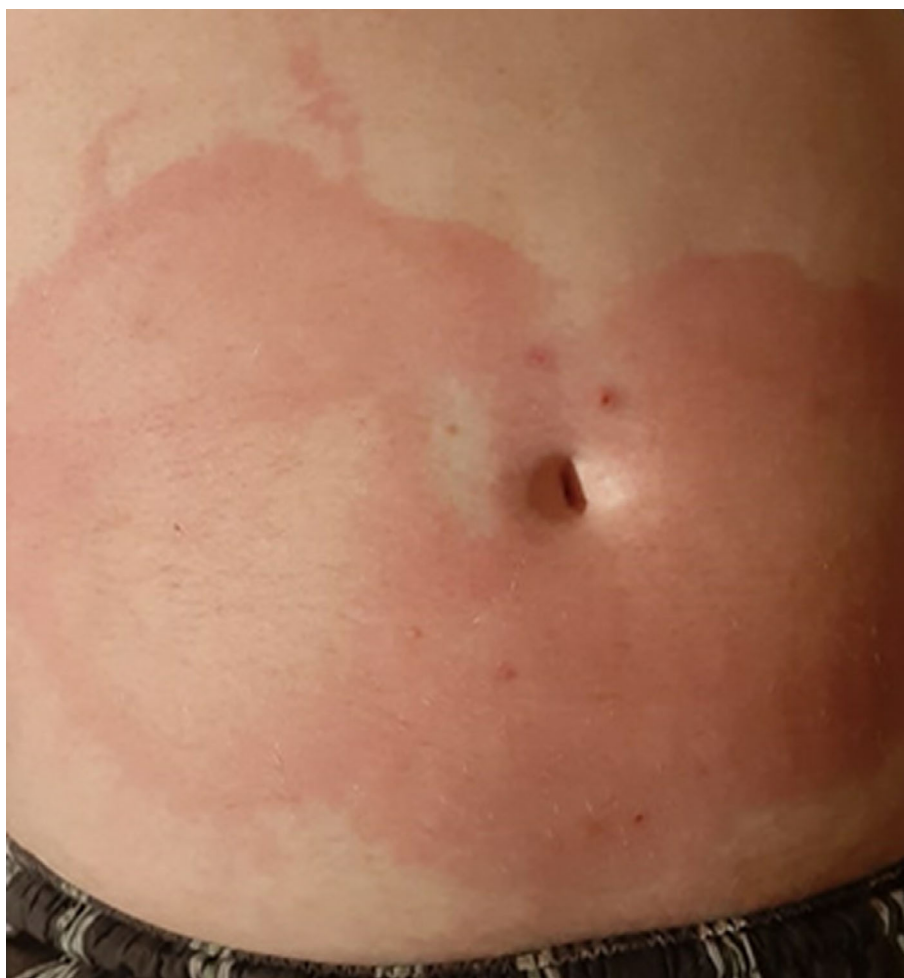


Figure 1 Periumbilical erythema 1 day after second injection of dupilumab (picture taken by the patient).

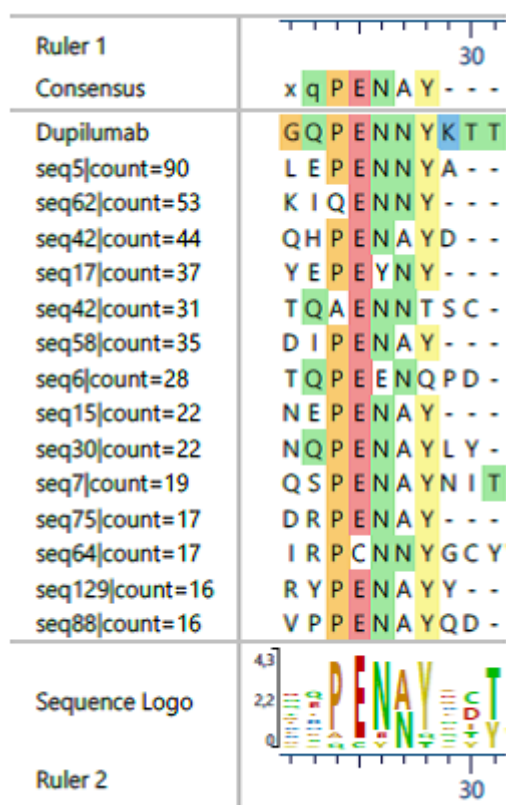


Figure 2 Epitope by numbers: Alignment of sequences enriched by binding to patients serum antibodies: Shown are only the most frequently observed ('count=') sequences sharing fractions of the PENNY motif with the dupilumab sequence (top). The EPENNY sequences are much more enriched than the QPENNY sequences. In all sequences, the E (glutamic acid) is found almost four times more frequently preceding the PENNY variations than Q (Glutamin). The probability to identify EPENNY once is 1 in 53 667 330 sequences but it is found 90 times in only 332 472 sequenced peptide genes.

most frequent adverse reactions include injection site reactions and conjunctivitis/blepharitis.^{1,2} Recently, a case with suspicion of an IgE-mediated hypersensitivity was reported.³ We herein report upon a patient who developed serum sickness-like reaction (SSLR) under therapy with dupilumab.

This 54-year-old male patient with longstanding AE was under cyclosporine therapy when first presenting in our university department. Due to severe AE (SCORAD 56), we started him on dupilumab (Sanofi-Genzyme, Berlin, Germany, 2 × 300 mg subcutaneously) and cyclosporine was tapered down. Ten days later, he developed fever, chills and arthralgia as well as large erythema with lymphangitis at injection sites (Fig. 1). Symptoms rapidly improved under self-medication with metamizol. At day 12, he chose to inject dupilumab (300 mg) ahead of the regular schedule, and within hours, he

developed a comparable clinical picture as after first injection. When presenting in our clinic at day 18, he was in good general condition with AE having slightly improved.

There was an increase of C-reactive protein (36.98 mg/L, <5) and of gamma globulins (polyclonal, 28.2%; 10.2–18.7). Total serum IgG was 20.3 g/L (7.0–16.0) with increase of IgG1 (14.9 g/L, 0.05–1.25). Total IgE was 612 kU/L, serum IgA was not detectable. Cyclic citrullinated peptides were positive complement factor C4 was decreased (0.11 g/L, 0.18–0.49). Within normal range were circulating immune complexes, C3, antinuclear antibodies, rheumatic factor, liver enzymes, creatinine and urine analysis. Skin biopsy showed dense lymphocytic peri- and intravascular infiltrates. About 4 weeks later, skin prick test with dupilumab, including late readings, was negative.

Using a recently described phage display method,⁴ we identified two epitopes within the heavy chain of dupilumab to which there was binding of antidrug antibodies (ADA) in the patient's serum. One was identified at 164-VSWNS-168 (V-valine, S-serine, W-tryptophan and N-asparagine) of the IgG4 heavy chain Fc1 region, and another stretched along 391-QPENNY-396 (Q-glutamine, P-proline, E-Glutamic acid, N-asparagine and Y-tyrosine) of the Fc3 domain. Both are marked in bold in the following amino acid sequence⁵ of the heavy chain of dupilumab:

EVQLVESGGGLEQPGGSLRLSCAGSGFTFRDYAMTWVRQ
APGKGLEWVSSISGSGGNTYYADSVKGRFTISRDN SKNTLYL
QMNSLR AEDTAVYYCAKDRLSITIRPRYYGLDVWGQGTTVT
VSSASTKGPSVFPLAPCSRSTSESTAALGLVKDYFPEPVT**VS**
NSGALTSGVHTFPAVLQSSGLYSLSSVTVPSSSLGKTQYTCN
VDHKPSNTKVKDRVESKYGPCCPPCAPEFLGGPSVFLFPPK
PKDTLMISRTPEVTCVVDVSDQEDPEVQFNWYVDGVEVHN
AKTKPREEQFNSTYRVVSVLTVHLQDNLNGKEYCKKVS NK
GLPSSIEKTISKAKGQPREPQVYTLPPSQEEMTKNQVSLTCL
VKGFYPSDIAVEWESNG**QPENNY**KTTTPVLDSDGSFFLYS
RLTVDKSRWQEGNVFSCSV MHEALHNHYTQKSLSLSLG.⁵

Enriched sequences similar to this part of the antibodies constant region contain preferably glutamic acid (E) instead of glutamine (Q) (Fig. 2). As deamidation reactions turning the acid amide of Q into the free acid resulting in E are common,⁶ antigens causing the patient's ADA are most likely traces in the dupilumab preparation containing a deamidated glutamine (Q), i.e. glutamic acid (E).

Under the diagnosis of SSLR to dupilumab, the patient was started on oral baricitinib (off-label). SSLR is similar to classic serum sickness (CSS), a type-III immune complex hypersensitivity reaction.^{7,8} In CSS, antibodies develop 6–10 days after allergen contact and deposition of antigen–antibody complexes with complement activation leads to fever, lymphadenopathy, arthralgias, cutaneous eruptions, gastrointestinal disturbances and proteinuria.⁸

SSLR resembles CSS with regard to elicitors, symptoms and time course but it is caused by different, so far poorly understood, mechanisms. As in our case, circulating immune

complexes typically cannot be found in SSLR and hepatic involvement is rare.^{7,8}

The newly diagnosed selective IgA deficiency (sIgAD) may have been a predisposing factor for SSLR in our patient, because autoimmune diseases, including CSS, were shown to be associated with primary immunodeficiencies.⁹

Several drugs (i.e. rituximab and omalizumab)^{9,10} were reported to induce SSLR. According to summary of product characteristics for dupilumab, during development program of this drug, two subjects with AE experienced CSS or SSLR.¹

In summary, we report on a rare case of SSLR under therapy with dupilumab. Epitopes for patient's autoantibodies binding to the heavy chain of this drug were identified by phage display.

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The patient in this manuscript has given written informed consent to publication of the case details.

Conflicts of interest

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Hidradenitis suppurativa – prevalence analyses of German statutory health insurance data

Editor

Hidradenitis suppurativa (HS) is a chronic, inflammatory disease affecting the intertriginous skin of axillary, inguinal and perianal sites.¹ In these areas, patients develop painful and disabling skin lesions such as inflamed nodules, abscesses and fistula with foul-smelling secretions. We aimed to investigate the documented prevalence and health care of HS patients in Germany. Therefore, we analysed a data set from a German nationwide statutory health insurance (SHI). The utilized database contains information of 2.8 million individuals, representing 4% of all insured individuals of the German SHI system. In order to identify patients suffering from HS, the codification of the ICD-10 (German modification) and drug prescriptions were used. It was stated that a patient suffers from HS (Groups 1/2) if there was at least one documented occurrence of ICD L73.2 in the inpatient and/or outpatient sector of the database, with the coding quality: 'confirmed diagnosis' or 'asymptomatic condition diagnosis'. Additionally, patients with ICD L73.2 and coding quality 'suspected diagnosis' (Groups 3/4) and patients with potential misdiagnoses (Groups 5/6) were identified (Table 1). PZN numbers (unique identifiers applied to code drugs in the outpatient sector) were used to identify patients who received drug therapy according to HS guidelines (Groups 1/3/5) or not (Groups 2/4/6). The considered drugs were clindamycin, rifampicin, minocycline, acitretin, isotretinoin, dapsone, infliximab and adalimumab. For analysis of HS prevalence, a 3-year period (2010–2012) was chosen because of the chronic and undulating character of HS, allowing for inclusion of individuals who were asymptomatic for a few months after treatment. Analyses of outpatient/inpatient care and sickness benefits were based only on data from 2012.

2650 patients with a diagnosis of HS (Groups 1/2) were identified in the database, yielding a prevalence of 0.09% (Table 1). Groups 3/4 contained a smaller patient population and might increase the HS prevalence by 0.01% only. The calculated